Amendments to the Drawings:

Please amend the drawings as follows:

Replace Figure 2 with the corrected Figure 2 on the attached replacement sheet.

REMARKS

Status of the Claims

Claims 1-31 are pending. Claims 23-31 were withdrawn from consideration by the Examiner. Claims 1-22 were rejected. Claim 18 was deemed allowable but objected to for depending from a rejected claim. Claims 1-31 are subject to restriction and/or election requirement. Applicants thank the Examiner for withdrawing all previously asserted claim rejections under 35 U.S.C. § 103(a). See Office Action, page 10.

Amendments to the Claims

Claims 1, 5 and 19 were amended in this reply. All amendments were done to improve and clarify the language of the claims. No new matter was added by the amendments.

Specifically, Applicants have amended claims 1 and 19 to claim more clearly and definitely a measurement step determining an L1-dependent measurement signal and a measurement step determining an L2-dependent measurement signal or an L1 plus L2-dependent measurement signal. These two measurement steps are performed at different time points (T1 and T2) or by different methods (method 1 and method 2). Amended claims 1 and 19 are supported by the previously presented claims 1 and 19, and throughout the specification, for example, at paragraphs [012], [018], and [050].

Applicants have amended step (iii) of claim 5 to simplify the language and to make it more concise. The amended claim 5 is supported by the previously presented claim 5 and the specification, for example, at paragraph [050].

Objections to the Specification

The Office objected to the disclosure because of alleged informalities in paragraphs [0131] and [0133]. Office Action, page 2. Applicants have addressed these objections by amending paragraphs [0131] and [0133].

In paragraph [0131], the unit of measurement "pl" was replaced with "µl." "pl" was an incorrect unit abbreviation due to a typographical error. The correct unit abbreviation ("µl") is supported by a comparison of Example 11 (in particular paragraph [0131]) and Example 12 (in particular paragraph [0133]). Paragraph [0133] describes a standard immunoassay which uses similar volumes than the immunoassay according to the invention described in paragraph [0131].

In paragraph [0131], one "and" word was replaced with a comma. This "and" word was superfluous because it was placed between the first and second elements of a recitation of three different elements.

Applicants disagree that the first sentence in paragraph [0133] has too many "and" words. In this paragraph, the first "and" word is correctly placed between the two elements in a recitation of two elements. The second "and" word is correctly placed between two equal parts of the principal clause. Applicants have added a comma after the end of the first part of the principal clause to clarify the grammatical structure of the sentence.

In the assays described in paragraphs [0131] and [0133] the signal is measured by luminescence. The label used in these assays is chemiluminescent particles, in particular C-bead-ADx-DxAI coated with anti-human IgG antibodies. C-bead-ADx are aminodextran-coated chemiluminescent particles. See specification, for example, at

paragraphs [078], [0103]-[0104] and [0114]-[0115]. The specification teaches that luminescence is used to measure the signal in an assay of the invention if the label used is a chemiluminescent substance. See specification, for example, at paragraphs 36, 54, and 58. Accordingly, Applicants added the words "by luminescence" at the appropriate locations in paragraphs [0131] and [0133].

Objections to the Drawings

The Office objected to Figure 2 as being too small, as having indistinguishable data points, and as having x-axis labels that do not align with anything. Office Action, page 3. In response, Applicants have provided a corrected drawing sheet that addresses these objections.

Rejections under 35 U.S.C. § 112

Claims 1-22 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Office Action, page 4. Applicants respectfully disagree. However, to expedite the prosecution of this application Applicants have amended claims 1, 5 and 19 as follows to address the Office's rejections.

Claims 1 and 19 have been amended to clarify that the binding partners R2 and R3 are selected for use in the claimed methods based on their predetermined differential properties relating to the saturation of their analyte A-binding sites. The determination of these differential properties is not itself part of the claimed method. Therefore, measurement of only one sample is sufficient to practice the claimed methods. This amendment is supported by the specification, for example, at paragraph

[012]. This amendment addresses the second last and third last paragraphs on page 4 of the Office Action.

Claims 1 and 19 have also been amended to clarify that the claimed methods require a measurement step determining an L1-dependent measurement signal and a measurement step determining an L2-dependent measurement signal or an L1 plus L2-dependent measurement signal (see above). These two measurement steps are performed at different time points (T1 and T2) or by different methods (method 1 and method 2). This amendment addresses the last paragraph on page 4 of the Office Action and paragraphs 1-4, 7 and 8 on page 5 of the Office Action.

The Office asserted that the term "hook effect" in claims 4 and 20 is indefinite. Office Action, page 5, paragraph 5. Applicants respectfully disagree. The term "hook effect" is clearly defined in the specification at paragraph [005]. Furthermore, the specification explains in detail how the claimed methods allow to detect, avoid or decrease a hook effect. See paragraphs [011] to [022]. Applicants in particular point the Office to paragraph [018] which spells out in practical terms how the methods allow to detect, avoid or decrease a hook effect. In addition, Figure 2 provides an example illustrating how the methods allow to detect, avoid or decrease a hook effect.

The Office asserted that step (iii) of claim 5 is incomprehensible. Office Action, page 5, paragraph 6. Applicants have now amended step (iii) of claim 5 to simplify the language and to make it more concise.

In light of all of the above, Applicants respectfully submit that claims 1-22 are not indefinite and request that the rejection of claims 1-22 under 35 U.S.C. § 112, second paragraph, be withdrawn.

Rejections under 35 U.S.C. § 102

Claims 1-10, 16, 17 and 19-22 were rejected under 35 U.S.C. § 102(b) as being anticipated by Palomäki. Among other things, the Office asserted that Palomäki describes a method comprising "determining analyte label-dependent signals using different methods at different times." Office Action, page 6. Applicants respectfully disagree at least for the following reasons.

The Office points to page 57, right column, fifth paragraph, of Palomäki to support the assertion that Palomäki describes a method comprising determining analyte label-dependent signals using different methods. Office Action, page 6, footnote 9. Specifically, the Office asserted that Palomäki uses two different methods to determine analyte label-dependent signals: (1) use of eyeball and (2) plate reader detectors. However, the paragraph cited by the Office does not contain any evidence or even suggestion that the analyte label-dependent signals are determined by use of eyeball. The fact that "colour development was allowed to proceed in the dark for 30 min" does not imply that the analyte label-dependent signals were then determined by use of eyeball. Rather, colour development is a precondition for measuring the analyte label-dependent signals in a highly sensitive microtitre plate reader as the one used by Palomäki. Use of eyeball would certainly not be sensitive and accurate enough to arrive at any meaningful determination of analyte label-dependent signals in a complex immunoassay designed to determine the presence of hepatitis B virus in patient samples, as the one described in Palomäki, and there is accordingly no indication that Palomäki did use eyeball for any such determination.

The Office points to page 58, right column, paragraph "Optimization...", of Palomäki to support the assertion that Palomäki describes a method comprising determining analyte label-dependent signals at different times. Office Action, page 6, footnote 10. Applicants respectfully disagree. The recited paragraph of Palomäki reads as follows:

> Optimization of the HBsAg EIA. The two one-step HBsAg EIA procedures showed similar sensitivity when the polyclonal enzyme tracer (HRP-Pab-HBsAg) at optimal concentration was used alone or simultaneously with the optimally diluted monoclonal enzyme tracer (HRP-Mab2-HBsAg); 0.6 and 0.3 ng/ml (standard procedure), 0.2 and 0.15 ng/ml (overnight procedure) for HBsAg/ay and HBsAg/ad subtypes, respectively (Fig.2). On the other hand, the sensitivity for subtype ay was only 3 ng/ml (standard procedure) and 0.4 ng/ml (overnight procedure) when the HRP-Mab2-HBsAg was used alone as the enzyme tracer.

Palomäki, page 58, column 2, paragraph 2.

Applicants respectfully submit that this paragraph does not describe any procedure that involves separate measurements of an individual sample. Rather, this paragraph describes the results of several separate EIA experiments that were carried out to optimize the conditions for the desired HBsAg EIA. The tested parameters included antibody type and antibody combination. These parameters were tested in two separate, one-step EIA procedures that used different incubation times (2 hrs or overnight). No more than one separate measurement appears to have been taken for any individual sample.

However, the rejected claims of the instant invention at least require two separate measurements of a sample taken either at different time points (T1 and T2) or by different methods (method 1 and method 2). Measurement No. 1 measures an L1-

dependent signal. Measurement No. 2 measures an L2-dependent signal or an L1 plus L2-dependent signal. Applicants have amended claims 1 and 19 to claim more clearly and definitely describe these two separate measurements of a sample (see above).

Palomäki teaches a method that involves a single measurement of absorbances at 450 nm (Palomäki, page 57, column 2, paragraph 5.) ("The reaction was stopped by adding 100 µl of 1 N H_2SO_4 and absorbances at 450 nm were then measured using the Titertek Multiscan MCC/340 microtitre plate reader (Labsystems)") The fact that the word "absorbances" is in the plural form relates to the presence of multiple samples on the microtitre plate, whereby each sample is in a different well. (Palomäki, page 57, column 2, paragraph 5.) ("Test samples and controls (50 µl) were added to the microtitre wells simultaneously with the HRP-Pab-HBsAg- and the HRP-Mab2-HBsAg-conjugates (50 µl)...") The plural form does not indicate that more than one measurement is taken for any individual sample.

Furthermore, Palomäki emphasizes the importance of using polyclonal and monoclonal HRP-coupled antibodies simultaneously. (Palomäki, for example, page 55, title and abstract; page 57, column 2, paragraph 3; and page 62, paragraph 4.) Moreover, the polyclonal and monoclonal antibodies are both labelled with the same horseradish peroxidase (HRP). (Palomäki, page 57, column 1, paragraph 3.) Therefore, the single absorbance measurement at 450nm captures the signals of both antibodies simultaneously.

In summary, the method described by Palomäki involves a single measurement of an individual sample that simultaneously measures the signals of the two HRP-labelled antibodies by the same method. Hence, when compared to the method of the

instant invention, the measurement of Palomäki provides only one of the measurements required by the claim. Because the independent claims 1 and 19 of the instant invention set forth two separate measurements (i.e. Measurement No. 1 and No. 2), Palomäki does not describe, expressly or inherently, each and every element of claims 1 or 19. However, "[a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." M.P.E.P. § 2131. Applicants therefore respectfully submit that Palomäki cannot anticipate independent claims 1 or 19 of the instant invention.

In light of the above, Applicants respectfully submit that claims 1-10, 16, 17 and 19-22 are not anticipated by Palomäki and request that their rejection under 35 U.S.C. § 102(b) be withdrawn.

Claims 1-3, 7, 9-12, 16 and 17 were rejected under 35 U.S.C. § 102(b) as being anticipated by Klein et al. The Office asserted that Klein et al describe a method comprising (1) incubating a sample with a binding partner associated with a solid phase, and binding partners associated with labels, wherein the binding partners have different affinity towards analyte; and (2) determining analyte label-dependent signals using different methods at different times. Office Action, page 8. Applicants respectfully disagree at least for the following reasons.

The Office alleges that "Binding ligand" in Figure 1 represents a "binding partner associated with a solid phase." Office Action, page 8, footnote 16. However, "Binding ligand" in Figure 1 is <u>not</u> associated with a solid phase. In Figure 1, only wheat germ agglutinin (WGA) is associated with a solid phase, the solid phase being controlled pore glass (CPG). See Klein et al., page 5336, second last paragraph ("As a model

system..."). Furthermore, "Binding ligand" in Figure 1 does not represent a "binding partner" as required by the claims of the instant invention, because "Binding ligand" is neither associated with a solid phase, a label, or a member X of a specific binding pair, nor does it have binding sites for an analyte that is to be detected by the described NMR method. Rather, "Binding ligand" itself represents a substance in a sample that is to be detected by the described NMR method. See Klein et al., Figure 1 legend ("A fast exchange equilibrium between receptor bound ligand and the free state allows the detection of these molecules in solution" (emphasis added)). Thus, "Binding ligand" in Figure 1 is more akin to an analyte to be detected in a sample than to a binding partner of such an analyte.

The Office further alleges that "Binding ligand" in Figure 1 also represents "binding partners associated with labels." Office Action, page 8, footnotes 17 and 18. However, for the reasons outlined above the "binding ligands" depicted in Figure 1 do not represent binding partners as required by the claims of the instant invention. In addition, the "binding ligands" depicted in Figure 1 are not associated with a label according to the instant invention. The Office asserted that a hydrogen atom is a label that is associated with the "binding ligands". Office Action, page 8, footnote 18. However, the hydrogen atom is an integral component of the "Binding ligand" molecules. It is therefore not associated with the "binding ligands" as defined by the instant invention. See specification, paragraph [035].

The Office further alleges that WGA in Figure 1 represents an analyte towards which the "binding ligands" (as "binding partners") have different affinities. Office Action, page 8, footnote 19. However, WGA in Figure 1 does not represent an analyte

as required by the claims of the instant invention. An analyte of the instant invention is a substance in a sample that is to be detected by the claimed methods. See specification, paragraph [025]. In contrast, WGA in Figure 1 is itself chemically coupled to a solid support, CPG (see also Scheme 1 on page 5337). WGA represents a means of the described NMR method for detecting "binding ligands" in a solution. WGA does not represent a substance that is to be detected by the NMR method, as would be required if it were analogous to an analyte of the instant invention.

The Office further alleges that Figure 2 shows the use of different methods for determining analyte label-dependent signals. Office Action, page 8, footnote 20. However, none of the methods used in Figure 2 detects WGA which the Office contended represents the analyte. Rather, the methods detect one or several of the oligosaccharides in the test solution. See Klein et al., page 5337, Figure 2 legend. The oligosaccharides analyzed in Figure 2 correspond to the "Binding ligand" in Figure 1.

In sum, the method described by Klein et al. represents a method to detect binding of a ligand (for example, a oligosaccharide as in Figure 2) to an immobilized receptor (for example, WGA coupled to CPG). The ligand may be analogous to an analyte of the instant invention in the sense that it is the subject of a detection method. The method of Klein et al includes only one binding partner for the ligand, namely the immobilized receptor. The methods claimed in the instant invention require three different binding partners (R1, R2 and R3) for the analyte. Since the three binding partners are distinct elements of the claims, Klein et al can not anticipate the claims. To anticipate a claim, the reference must teach every element of the claim. MPEP § 2131.

In light of the above, Applicants respectfully submit that claims 1-3, 7, 9-12, 16 and 17 are not anticipated by Klein et al and request that their rejection under 35 U.S.C. § 102(b) be withdrawn.

Claims 1-3, 7, 9-17, 19, 21 and 22 were rejected under 35 U.S.C. § 102(a) as being anticipated by Meinecke & Meyer. The Office acknowledged that this rejection may be overcome by filing an English translation of foreign priority document DE 100 64 827.4 in accordance with 37 C.F.R. § 1.55 and in order to show that the rejected claims are supported by the priority claim. Office Action, page 9, footnote 22. Applicants now file concurrently herewith an English translation of foreign priority document DE 100 64 827.4 in accordance with 37 C.F.R. § 1.55. Accordingly, Applicants respectfully request that the rejection of claims 1-3, 7, 9-17, 19, 21 and 22 under 35 U.S.C. § 102(a) as being anticipated by Meinecke & Meyer be withdrawn.

Consideration of IDS References

Applicants noted that the Examiner did not consider two of the previously submitted IDS references, apparently due to perceived insufficiencies of the filed PTO/SB/08 form as indicated in hand-written notes on the form. Applicants now enclose a revised version of the same PTO/SB/08 form in which the hyperlinks to the two references were removed. The two references are publications by PerkinElmer, providing technical support to their customers. These publications are often available in technical libraries, or may be requested directly from the company. They are also posted on the Perkin-Elmer website, and will, of course, be part of the file wrapper of the present application. Applicants note that the previous Examiner in this case, Deborah A. Davis, considered the two references, as indicated by her initials dated

February 15, 2007. Applicants respectfully request that the current Examiner also consider the two references and indicate that they were considered by making appropriate notations on the attached form. While the two references were submitted previously, Applicants do not enclose courtesy copies herewith.

Conclusion

Applicants respectfully request the entry of this Reply by the Office, placing claims 1-22 in condition for allowance. In view of the foregoing remarks, Applicants submit that this claimed invention is not anticipated or indefinite. Applicants therefore request the Office's reconsideration of the application, and the timely allowance of the pending claims.

Request for Interview

Should the Office maintain the rejections, Applicants request that the Examiner contact the undersigned at 202-408-4086 so that a suitable date and time can be scheduled for an Examiner interview to clarify the issues remaining in this case.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

Dated: April 21, 2008

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